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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,396	12/27/2001	David Botstein	GNE.2930R1C4	1010

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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/033,396	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 16, 2007 has been entered.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 22-26 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of antibodies which bind to a protein termed Pro-539 (SEQ ID NO: 7) or portions thereof, in the specification, where the protein has the amino acid sequence of SEQ ID NO: 7.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the antibody or of the Pro-539 protein to which it binds. The cited utilities in the specification include overexpression in cancer. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the PRO 539 polypeptide or antibody. A review of the specification and of the prior art finds no well established utilities for unknown proteins and antibodies whose activity, whose enzymatic or other biochemical function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the antibody to PRO 539 protein which are identified in either the specification or in the prior art.

Abundant art supports the absence of a necessary relationship between mRNA and protein

This data further lacks any of the hallmarks of utility because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed

that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Further, given the breadth of these claims which encompass 95% identical molecules, there is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein

function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where the function of PRO-539 (SEQ ID NO: 7) is not known, the expectation is even lower that there is any utility that can be derived based upon the sequence.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression

Nine out of ten recent microarray papers show discordant protein and mRNA expression data

Nine recent papers provide much stronger evidentiary showings, showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Ornẗoft paper shows a counter example. Czupalla et al (Proteomics (2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing genes, Czupalla continues "In contrast, a second group of 70 gene products comprises those for which we did not observe any changes in mRNA expression although we could clearly detect either increased or decresed protein expression by 2-DE (see page 3874, column 1)." The data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists.

Kwong et al (Genomics (2005) 26:142-158), drawn to colorectal cancer, a disease similar to the one analyzed by Appellant, has even stronger conclusions. Kwong notes that 47 genes had valid protein and mRNA data in the 10 samples and were selected for correlation analysis. Kwong states regarding these samples that "Only 12 of the 47 genes exhibited correlated expression at a significance level less

than 0.05. Surprisingly, 13 genes had a negative correlation between mRNA and protein levels. The correlation between protein and mRNA was also compared on a sample-by-sample basis. Of the 53 samples for which data was available, mRNA and protein levels were found to be correlated at a significance level of 0.05 in only 14 samples, while 14 mRNA and proteins were negatively correlated (see page 151, column 2 to page 152, column 1). Following Kwong, it is clear that it is not more likely than not that protein and mRNA expression are correlated. In fact, Kwong supports the conclusion that it is more likely than not that there is no correlation.

Chen et al (Mol. Cellular Proteomics (2002) 304-313 notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. (see page 311, column 1)" Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levles and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values (see page 311, column 1)." Chen does refer to Celis (ref. 19 of Chen) who cites Orntoft et al who shows 39 out of 40 proteins correlated in expression between the mRNA and protein levels.

Conrad et al (Mol. Cell Proteomics (2005) 4(9) :1284-1296) performed an analysis on 2501 proteins of which data regarding the abundance of 1900 proteins was aligned with nucleic acid microarray data(see page 1290, column 1). Conrad found that

in this very large data set "There is little correlation between RNA and protein abundance identified and predicted by cICAT (see page 1290, column 2)."

Ginestier et al (Am. J. Pathol. (2002) 161:1223-1233) teaches at table 4 that only five out of 15 genes showed concordance. Ginestier notes "For a category of molecules we found important differences between RNA and proteine xpression levels (see page 1230, column 2)."

Anderson et al (Electrophoresis (1997) 18:533-537) shows that for 19 proteins that were compared between 2D gel electrophoresis and mRNA analysis "the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0) (see page 536, column 1)." In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data. This is consistent with the showing of Washburn (Proc. Natl. Acad. Sci. (2003) 100 (6):3107-3112, who analyzed a comparison of 678 loci and found a correlation of 0.45 (see page 3109, column 1), which also shows a correlation that is closer to the absence of correlation than to a positive correlation.

Lee et al (Biotechnology and Bioengineering) (2003) 84(7):834-841) teaches "A key feature of all the observations and a common issue raised in the discussion of such results is the lack of an obvious linear correlation between mRNA expression and protein expression (see page 834, column 2). Commenting on their own data, Lee notes "Consistent with observation in other organisms, we observed no clear

relationship between mRNA amplification and protein amplification factors for Escherichia coli (see page 838, column 1)."

Provenzani et al (Carcinogenesis (2006) 27(7) : 1323-1333) shows a comparison of total mRNAs and mRNAs in the polysomal RNA, which are the mRNAs which will undergo translation into protein (see figure 2). Provenzani points out that a difference in polysomal loading will result in a difference in protein expression that is unrelated to the amount of mRNA being expressed. Provenzani notes "In this framework, our analysis shows that 80% of the genes undergoing a gene expression change in the transition between SW480 and SW620 cells do it by varying their degree of polysomal loading, implying a dramatic subversion in the signalling control of translation and/or in the translational machinery itself (see page 1330, column 1)." Provenzani explains this by stating "An impliciation of this possiblity would be a lack of correlation between transcriptomic and proteomic data in teh same sample (see page 1330, column 1)." Thus, Provenzani also supports the conclusion that up to 80% of genes will not show differential expression based upon mRNA level, but rather based upon polysomal loading, so that mRNA level will not provide significant information regarding the utility, or lack thereof, for the protein.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Statistical Significance

The overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant. While the specification states "Only values that were above this cutoff ratio were determined to be significant" in paragraph 0930, there is no evidence to suggest that this overexpression is statistically significant.

Further, there is no evidence that the overexpression was reproducible. From the data presented in the specification, a single prostate tumor sample from a single patient may have been used. Such a result from a single patient would not support any utility because even if the nucleic acid was overexpressed in the one patient, there would be no expectation that the result would appear in even one other patient, so there is no evidence of record that the overexpression shown has any utility as a diagnostic or for any other purpose. Also, there is no evidence that the overexpression in the prostate tumor was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note

that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene. Given the absence of any evidence regarding sample size and the absence of any direct association with Pro539 and lung tumors, this gene represents noise. The prior art suggests that such genes should not be placed on the array. Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays.

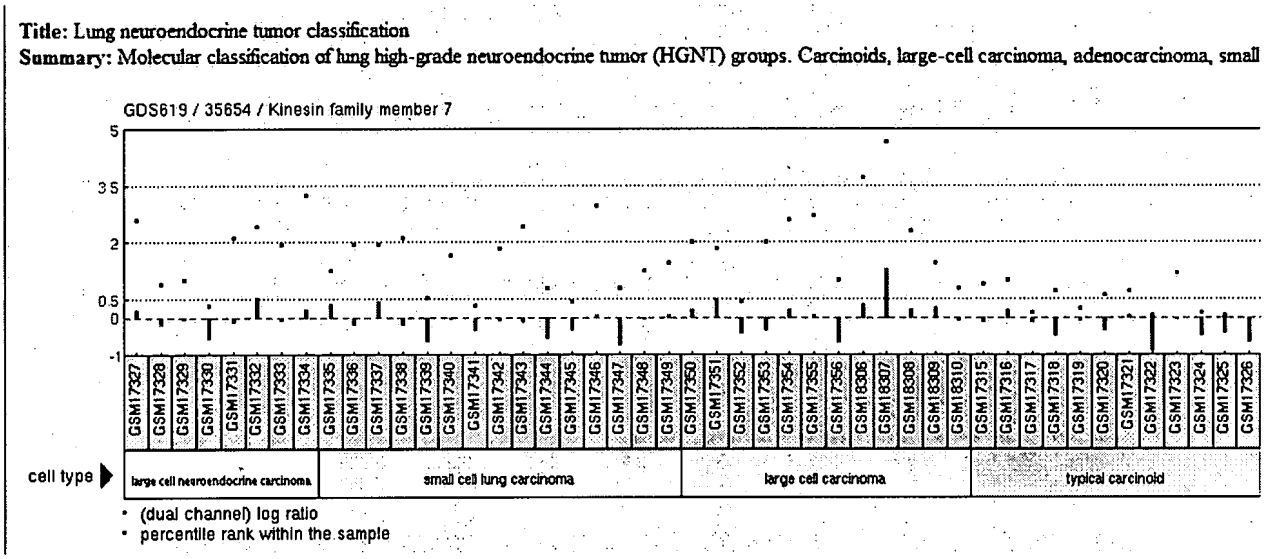
Absence of tissue matched controls

It is important to note that the gene encoding PRO539 was not found to be amplified in other listed tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 115). Therefore, the overexpression data itself is questionable, since blood and lung may naturally express PRO539 at different levels. The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy. Given these details, one skilled in the art would not conclude that the gene encoding PRO1269 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Gokman-Polar.).

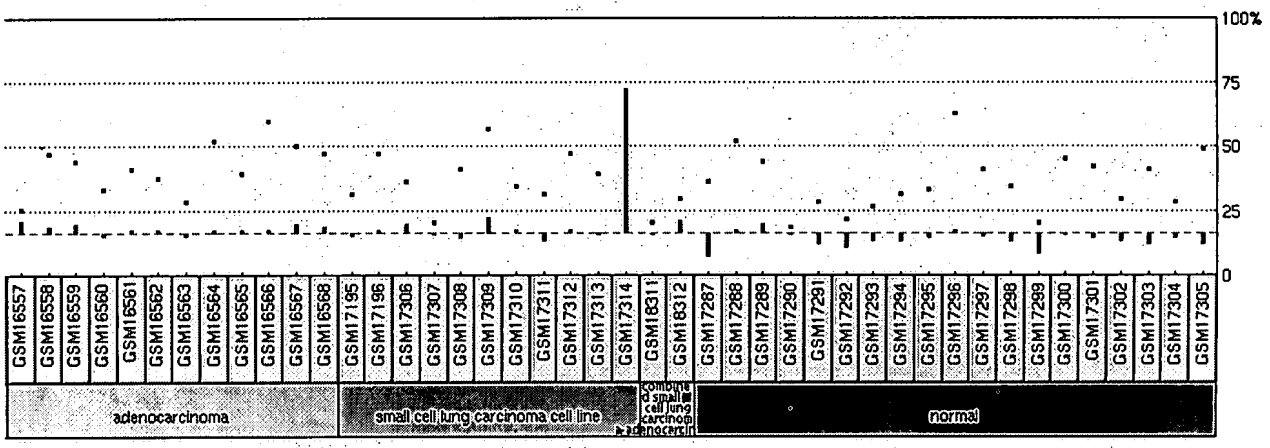
Specific data shows that Pro539 is NOT overexpressed in lung tumors.

Since the filing date of this application, a number of studies have analyzed genes to determine overexpression in lung tumors relative to normal controls. Some of these have posted the entirety of their data sets to the NCBI website at

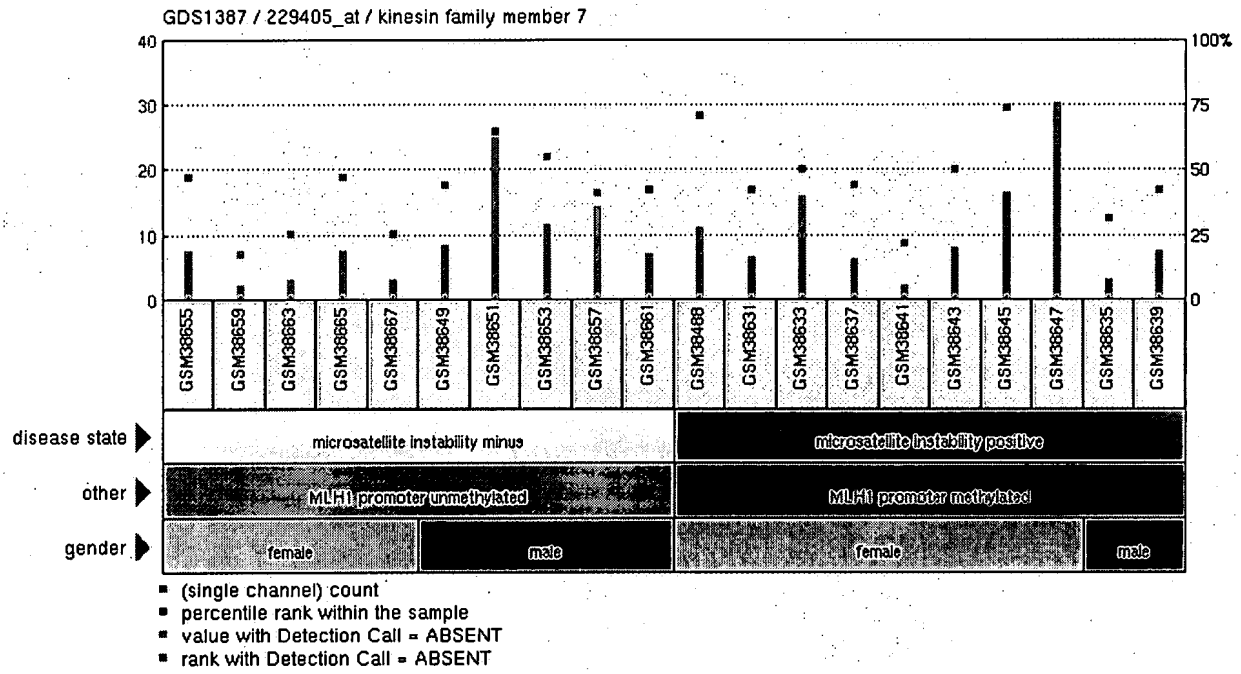
http://www.ncbi.nlm.nih.gov/geo/. Several specific analyses demonstrate that Pro539, which is known as Kif7, is not overexpressed in lung tumors. Two such analyses are shown below. As the first analysis shows (on a proprietary array), titled, Lung neuroendocrine tumor classification, the Kif7 gene expression is all over the map. There is no correlation whatsoever between expression and cancer. In the second analysis (on the U133 affymetrix array), colorectal carcinoma samples were analyzed and again, the data appears to show no relationship with cancer.



l-cell lung carcinoma cell lines, and normal lung examined.



Title: Colorectal carcinoma subtype with microsatellite instability (HG-U133B)
Summary: Comparison of colorectal carcinoma specimens positive and negative for microsatellite instability (MSI). Results also cor
of MMR genes results in MSI.



Therefore, given the specific data for PRO539 itself which demonstrates that in two different experiments on two different arrays with multiple samples, the nucleic acid was not overexpressed, there is no reason to believe that the protein would be overexpressed.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is also similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539 antibodies and proteins. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for the antibody to the PRO-539 protein of SEQ ID NO: 7. The antibody to the protein, as distinguished from the nucleic acid, has not been associated with any disease, any condition, or any other specific feature. There is no association of the antibody or protein with cancer or with any other disease. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein or antibody. A protein or antibody cannot be used to detect changes in its cognate nucleic acid, as shown by the Gokman-Polar and Meric papers, where protein levels are not correlative with nucleic acid levels. Therefore, there is no specific utility for this protein until a specific ligand is identified.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

Claim Rejections - 35 USC § 112 – Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to an antibody to the PRO-539 protein of SEQ ID NO: 7. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass not only a particular PRO-539 antibody but also include any antibody which binds the polypeptide of SEQ ID NO: 7.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and nucleic acids. It would require significant study to identify the actual function of the PRO-539 protein and nucleic acid, and identifying a use for this protein and resultant antibody would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

Abundant art supports the absence of a necessary relationship between mRNA and protein

This data further lacks any of the hallmarks of utility because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA

stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by

Applicant showing overexpression of one component does not provide utility for the protein itself.

Further, given the breadth of these claims which encompass 95% identical molecules, there is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where the function of PRO-539 (SEQ ID NO: 7) is not known, the expectation is even lower that there is any utility that can be derived based upon the sequence.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539. As noted in the

utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression

Nine out of ten recent microarray papers show discordant protein and mRNA expression data

Nine recent papers provide much stronger evidentiary showings, showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Orntoft paper shows a counter example. Czupalla et al (Proteomics (2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing genes, Czupalla continues "In contrast, a second group of 70 gene products comprises those for which we did not observe any changes in mRNA expression although we could clearly detect either increased or decresed protein expression by 2-DE (see page 3874, column 1)." The data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the

conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists.

Kwong et al (Genomics (2005) 26:142-158), drawn to colorectal cancer, a disease similar to the one analyzed by Appellant, has even stronger conclusions. Kwong notes that 47 genes had valid protein and mRNA data in the 10 samples and were selected for correlation analysis. Kwong states regarding these samples that "Only 12 of the 47 genes exhibited correlated expression at a significance level less than 0.05. Surprisingly, 13 genes had a negative correlation between mRNA and protein levels. The correlation between protein and mRNA was also compared on a sample-by-sample basis. Of the 53 samples for which data was available, mRNA and protein levels were found to be correlated at a significance level of 0.05 in only 14 samples, while 14 mRNA and proteins were negatively correlated (see page 151, column 2 to page 152, column 1). Following Kwong, it is clear that it is not more likely than not that protein and mRNA expression are correlated. In fact, Kwong supports the conclusion that it is more likely than not that there is no correlation.

Chen et al (Mol. Cellular Proteomics (2002) 304-313 notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. (see page 311, column 1)" Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levles and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression

values (see page 311, column 1)." Chen does refer to Celis (ref. 19 of Chen) who cites Orntoft et al who shows 39 out of 40 proteins correlated in expression between the mRNA and protein levels.

Conrad et al (Mol. Cell Proteomics (2005) 4(9) :1284-1296) performed an analysis on 2501 proteins of which data regarding the abundance of 1900 proteins was aligned with nucleic acid microarray data(see page 1290, column 1). Conrad found that in this very large data set "There is little correlation between RNA and protein abundance identified and predicted by cICAT (see page 1290, column 2)."

Ginestier et al (Am. J. Pathol. (2002) 161:1223-1233) teaches at table 4 that only five out of 15 genes showed concordance. Ginestier notes "For a category of molecules we found important differences between RNA and proteine xpression levels (see page 1230, column 2)."

Anderson et al (Electrophoresis (1997) 18:533-537) shows that for 19 proteins that were compared between 2D gel electrophoresis and mRNA analysis "the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0) (see page 536, column 1)." In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data. This is consistent with the showing of Washburn (Proc. Natl. Acad. Sci. (2003) 100 (6):3107-3112, who analyzed a comparison of 678 loci and found a correlation of 0.45 (see page 3109, column 1), which also shows a correlation that is closer to the absence of correlation than to a positive correlation.

Lee et al (Biotechnology and Bioengineering) (2003) 84(7):834-841) teaches "A key feature of all the observations and a common issue raised in the discussion of such results is the lack of an obvious linear correlation between mRNA expression and protein expression (see page 834, column 2). Commenting on their own data, Lee notes "Consistent with observation in other organisms, we observed no clear relationship between mRNA amplification and protein amplification factors for Escherichia coli (see page 838, column 1)."

Provenzani et al (Carcinogenesis (2006) 27(7) : 1323-1333) shows a comparison of total mRNAs and mRNAs in the polysomal RNA, which are the mRNAs which will undergo translation into protein (see figure 2). Provenzani points out that a difference in polysomal loading will result in a difference in protein expression that is unrelated to the amount of mRNA being expressed. Provenzani notes "In this framework, our analysis shows that 80% of the genes undergoing a gene expression change in the transition between SW480 and SW620 cells do it by varying their degree of polysomal loading, implying a dramatic subversion in the signalling control of translation and/or in the translational machinery itself (see page 1330, column 1)." Provenzani explains this by stating "An impliciation of this possiblity would be a lack of correlation between transcriptomic and proteomic data in teh same sample (see page 1330, column 1)." Thus, Provenzani also supports the conclusion that up to 80% of genes will not show differential expression based upon mRNA level, but rather based upon polysomal loading, so that mRNA level will not provide significant information regarding the utility, or lack thereof, for the protein.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Statistical Significance

The overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant. While the specification states "Only values that were above this cutoff ratio were determined to be significant" in paragraph 0930, there is no evidence to suggest that this overexpression is statistically significant.

Further, there is no evidence that the overexpression was reproducible. From the data presented in the specification, a single prostate tumor sample from a single patient may have been used. Such a result from a single patient would not support any utility because even if the nucleic acid was overexpressed in the one patient, there would be no expectation that the result would appear in even one other patient; so there is no evidence of record that the overexpression shown has any utility as a diagnostic or for any other purpose. Also, there is no evidence that the overexpression in the

prostate tumor was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene. Given the absence of any evidence regarding sample size and the absence of any direct association with

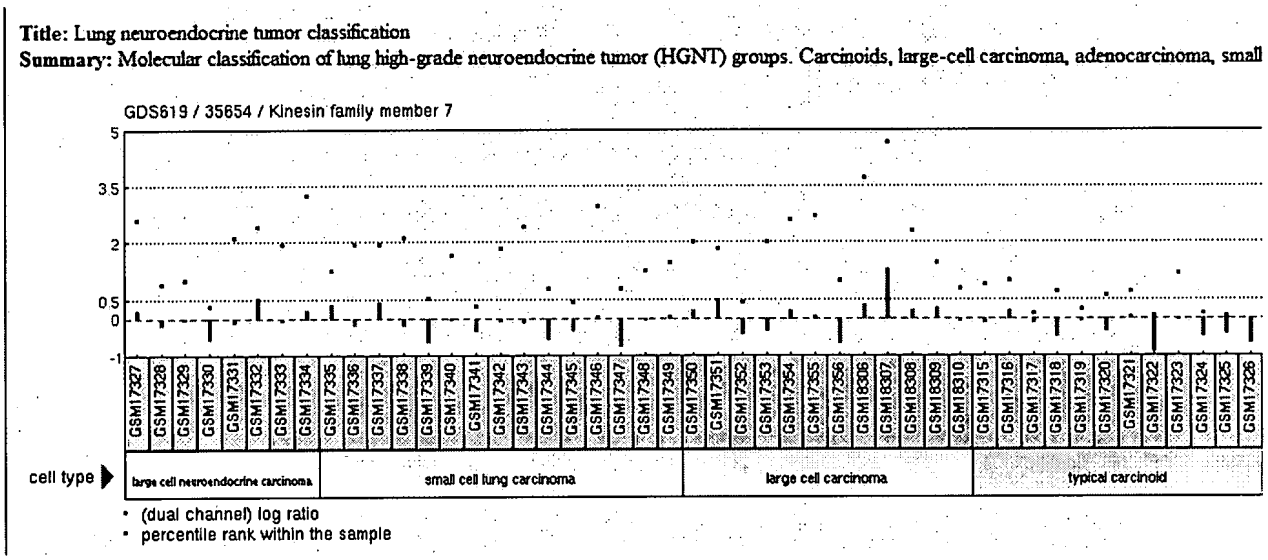
Pro539 and lung tumors, this gene represents noise. The prior art suggests that such genes should not be placed on the array. Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays.

Absence of tissue matched controls

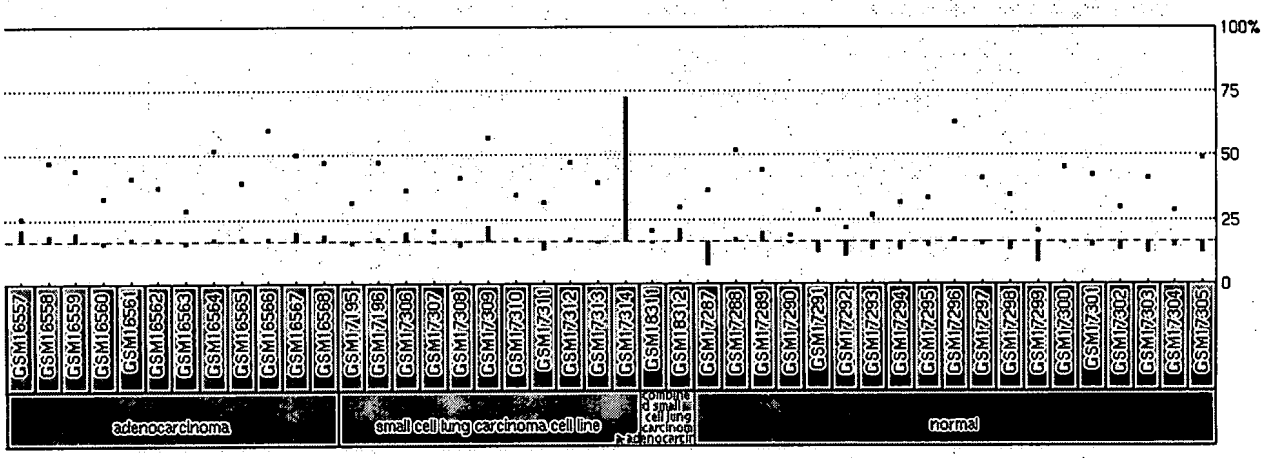
It is important to note that the gene encoding PRO539 was not found to be amplified in other listed tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 115). Therefore, the overexpression data itself is questionable, since blood and lung may naturally express PRO539 at different levels. The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy. Given these details, one skilled in the art would not conclude that the gene encoding PRO1269 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Gokman-Polar.).

Specific data shows that Pro539 is NOT overexpressed in lung tumors.

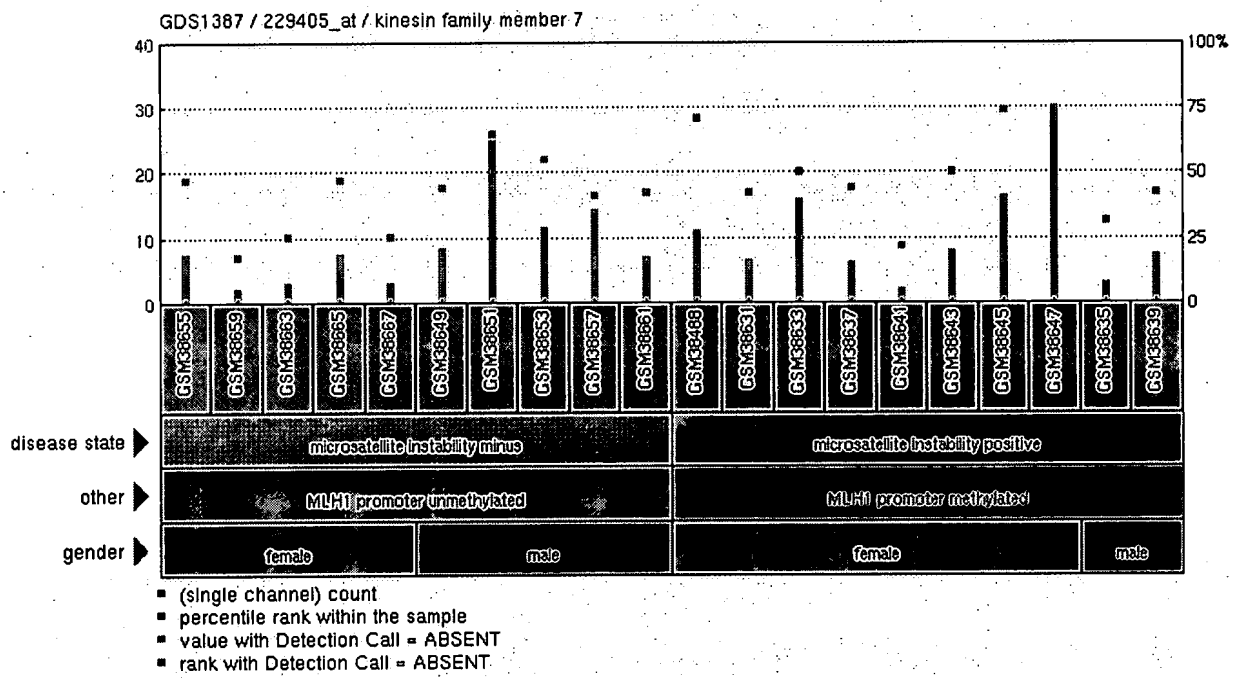
Since the filing date of this application, a number of studies have analyzed genes to determine overexpression in lung tumors relative to normal controls. Some of these have posted the entirety of their data sets to the NCBI website at http://www.ncbi.nlm.nih.gov/geo/. Several specific analyses demonstrate that Pro539, which is known as Kif7, is not overexpressed in lung tumors. Two such analyses are shown below. As the first analysis shows (on a proprietary array), titled, Lung neuroendocrine tumor classification, the Kif7 gene expression is all over the map. There is no correlation whatsoever between expression and cancer. In the second analysis (on the U133 affymetrix array), colorectal carcinoma samples were analyzed and again, the data appears to show no relationship with cancer.



l-cell lung carcinoma cell lines, and normal lung examined.



Title: Colorectal carcinoma subtype with microsatellite instability (HG-U133B)
Summary: Comparison of colorectal carcinoma specimens positive and negative for microsatellite instability (MSI). Results also cor
of MMR genes results in MSI.



Therefore, given the specific data for PRO539 itself which demonstrates that in two different experiments on two different arrays with multiple samples, the nucleic acid was not overexpressed, there is no reason to believe that the protein would be overexpressed.

Working Examples

The specification has no working examples that relate to the antibody or protein. The nucleic acid working examples, showing overexpression in certain cancer cell lines, are not relevant for the reasons given above. Specifically, there is no statistical showing that the overexpression of the nucleic acids is even significant in any way. Even if the nucleic acid data is deemed significant, there is no showing that the results from nucleic acids have any correlation with the protein or antibody and the art cited above demonstrates that there is no presumption of such a correlation.

Guidance in the Specification.

The specification provides no specific or substantial uses for the PRO-539 antibody or protein.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

6. Applicant's arguments filed March 16, 2007 have been fully considered but they are not persuasive.

Applicant's arguments were fully addressed in the previous final rejection.

Applicant takes issue with the disagreement over the Czupalla paper. Applicant argues that "they are not interested in predicting mRNA levels from changes in protein" so that this data is irrelevant. In fact, this is directly relevant because it goes to the question of whether mRNA level data is representative of protein level data. Applicant is relying upon the argument, which is strongly rebutted by 9 out of 10 papers, that mRNA expression is concordant with protein expression to show that this must be the case of Kif-7.

Applicant never presents any specific data on Kif-7 protein expression. Applicant never presents any specific data showing any feature, function, detail or activity of Kif-7. In fact, the specification does not even refer to the protein claimed as Kif-7, because the specification had no idea of the protein's function or activity when the application was

filed. Applicant attempts to make a generic argument that protein and mRNA expression is concordant.

Specific data is now presented in the rejections that shows that Kif-7, in at least two different experiments in multiple samples, does not appear to show any consistent pattern of overexpression relative to normal controls.

With regard to Czupalla, the fact the 47 proteins had concordant expression with their mRNAs does not void the fact that 70 proteins did not have concordant expression in Czupalla. Further, Applicant did not address the fact that over 1000 genes were found to be up or down regulated at the nucleic acid level, but most of these were not found (though this might be due to limitations in Czupalla's analysis).

Applicant then analyzes Chen's data, and argues that it is not relevant, nor is Kwongs, Conrad, Ginestier, Anderson. Each of these papers argues that mRNA and protein data, as measured globally, are not concordant. Applicant's arguments are contradicted by the conclusions drawn by the authors in each case. Therefore, the action relies upon the analysis of the authors of the papers.

Applicant admits that Washburn is relevant, but then attempts to distinguish Washburn by throwing out some of Washburn's data, without any justification. The flaw in Applicant's analysis here is not simply that Washburn disagrees in the conclusion, but that it is not the typical scientific method to discard data which disagrees with your hypothesis. Cherrypicking of Washburn's data could be performed to yield any desired result. The data as it is presented by Washburn does not support Applicant's position, but undeniably supports the conclusions of the rejection.

Finally, Applicant argues that the multple references cited are ignored. They are not ignored. They are given the proper weight. None of the references deals with global changes of mRNA or protein. Each deals with a specific protein or very small set of proteins. None of the references address the specific protein at issue, Kif-7, at all. These references do not overcome the prima facie case of utility and enablement.

The remaining arguments have been addressed multiple times in previous actions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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